vascular cell an amount of an antisense oligonucleotide consisting of consecutive nucleotides, the nucleotide sequence of which is set forth in SEQ ID NO:2, effective to reduce the levels of bcl-xL protein produced, thereby promoting the regression of vascular lesions, wherein one or more sugar of the oligonucleotide contain an -OMe group at its 2' position.--

--65. (New) An antisense oligonucleotide consisting of consecutive nucleotides, the nucleotide sequence of which is set forth in SEQ ID NO:2, wherein one or more sugar of the oligonucleotide is modified at its 2' position.--

A mark up copy of the amendments to the claims is attached hereto as **Exhibit A.**

REMARKS

Claims 9, 26-30, 32-36 are pending in the application. Claims 37-62, as recited in the Preliminary Amendment mailed January 9, 2002, are also pending but not yet ruled upon. By this Amendment applicant has amended claims 9, 26, and 36 and has added new claims 63, 64 and 65. After entry of this Amendment, claims 9, 26-30, and 32-65 will be pending. Applicant maintains that the amendments to the claims raise no issue of new matter. Support for the amended claims and new claims can be found in the specification as originally filed. Accordingly, applicant requests entry of this Amendment.

In an Office Action dated May 1, 2002 the Examiner stated that applicant's Preliminary Amendment mailed January 9, 2002 was not considered by the Examiner in rendering the [January 25, 2002]

Office Action because the Amendment had not reached the Examiner until after the Office Action had been prepared. The Examiner also stated that the Preliminary Amendment will not be treated as a Reply to the Office Action, but that applicant would be given the opportunity to submit a Supplemental Amendment within 30 days to address the issues raised in the Office Action.

In a telephone conference with the Examiner on May 17, 2002 applicant's attorney Peter Phillips inquired as to the status of the January 9, 2002 Preliminary Amendment, which was filed to present claims corresponding to U.S. Patent No. 6,172,216, within the one year period following issuance of that patent. Applicant was advised that the January 9, 2002 Preliminary Amendment was entered, and will be considered with applicant's response to the outstanding Office Action. It is applicant's understanding that the claims presented in the January 9, 2002 Preliminary Amendment comply with the one-year time period following issuance of U.S. Patent No. 6,172,216, in accordance with 35 U.S.C. §135(b).

Applicant wishes to inform the Examiner that the claims presented in the January 9, 2002 Preliminary Amendment were presented in a continuation application filed May 30, 2002. After applicant receives confirmation of the continuation application filing, applicant intends to cancel the corresponding claims 37-62 herein.

In the January 25, 2002 Office Action the Examiner stated that the remarks (page 4) section of the preliminary amendment filed 4-11-01, sets forth Robert Rando, and Joshua Ojwang as being co-inventors of the subject matter of claims 26-30. The Examiner also stated that applicant's remarks are uncertain since these claims have not been canceled, and neither Rando nor Ojwang appear as co-inventors on the Declaration submitted for this

application.

In response, applicant notes that claims 26-30 as presented here are directed to an improvement invented solely by Dr. Stein over an invention co-invented by Drs. Stein, Cossum, Rando and Ojwang. The "remarks" section regarding inventorship submitted in the Preliminary Amendment filed concurrently with the above-identified application was merely to inform the Examiner of the co-invented subject matter being claimed in U.S. Serial No. 09/832,633, filed concurrently with the above-identified application and also a continuation of 09/109,614, filed July 2, 1998. The "remarks" section was not intended to add or delete inventors. Dr. Stein is the sole inventor of the subject matter in claims 26-30 as pending in the subject application.

Claims Rejected Under 35 U.S.C. § 103

The Examiner stated that claims 9 and 36 are drawn to a composition comprising an antisense oligonucleotide comprising consecutive nucleotides, the nucleotide sequence of which is set forth in one of SEQ ID NOS: 1-13. The Examiner also stated that Claims 26-30 are drawn to a method of promoting the regression of vascular lesions comprising introducing antisense oligonucleotides shown to be effective in reducing bcl-x_L expression into a vascular cell.

The Examiner stated that Pollman teach inhibition of neo-intimal cell bcl-x expression comprising transfecting a composition comprising Lipofectamine and an antisense oligonucleotide directed against bcl-x into atheromatous (i.e. vascular) lesions in the rabbit carotid artery (Methods section, p. 226). The Examiner stated that specific down regulation of the bcl-x_L splice isoform resulted in regression of atheromatous lesions

(see Figure 8, page 226). The Examiner stated that, additionally, Pollman et al. discloses 3 phosphorothioate modified antisense oligonucleotides, wherein antisense sequence-3 (#3; see Methods section, page 226) comprises the consecutive nucleotide sequence of SEQ ID NO: 2 of the instant application and that Gibbons et al. teach a method for reducing the dimensions of a neointimal vascular lesion in a patient comprising localized delivery of an antisense oligonucleotide that inhibits the expression of bcl-x_L (col.2 lines 28-42). The Examiner stated that Gibbons et al. teach administration of antisense oligonucleotides comprising methods known in the art for enhancing the uptake of nucleic acids by cells, for example delivery systems include Sendai virus-liposomes, cationic liposomes polymeric gels or matrices, and porous balloon catheters (col. 7, lines 45-60). Additionally, the Examiner stated that Gibbons et al. teach that the antisense oligonucleotides used in the method for reducing the expression of bcl-x_L in cells may comprise modifications to enhance oligonucleotide intracellular stability and binding affinity. The Examiner further stated that a specific embodiment Gibbons et al. teach that the 2'-OH ribose sugar may be altered to form 2'-O-methyl (col. 5, lines 6-28). The Examiner also stated that since the specification as filed does not clearly define what the term "-OME" is intended to encompass, this term is interpreted as encompassing either "2'-O-methyl" or "2'-O-methoxy." The Examiner stated that furthermore, neither Pollman et al. nor Gibbons et al. teach the administration of antisense oligonucleotides into cells comprising the use of porphyrin as a delivery agent.

The Examiner stated that Manoharan et al. teach the design and use of derivatized antisense oligonucleotides, wherein derivatization of said antisense oligonucleotides results in improved transfer across cellular membranes (page 5, lines 7-9). The Examiner stated that the compounds of Manoharan et al.

comprise a plurality of linked nucleosides wherein at least one of the nucleosides is functionalized at the 2' -position with a substituent such as for example, a steroid molecule, a lipid soluble vitamin, a lipophilic molecule and a porphyrin (page 5, lines 20-30).

The Examiner stated that it would have been obvious to one of ordinary skill in the art, at the time of filing, to modify the teachings of Pollman et al. and Gibbons et al. with the teachings of Manoharan et al. in the design of a method comprising the use of a porphyrin compound in the delivery of antisense oligonucleotides targeting bcl-x_L to vascular lesions. The Examiner further stated that one of ordinary skill in the art would have been motivated to modify the method of delivering antisense oligonucleotides as disclosed by Pollman et al. and Gibbons et al. by the use of a porphyrin compound since the antisense oligonucleotides of Pollman et al. and Gibbons et al. are intended for delivery into cells, and the modifications taught by Manoharan et al. are disclosed as being useful to confer enhanced cellular uptake to the derivatized oligonucleotide compound. The Examiner stated that, furthermore, it would have been therapeutically advantageous to modify the method disclosed by Pollman et al. and Gibbons et al. by adding a modification that would increase the intracellular availability of the antisense compounds within the tissues to which the compound is administered. The Examiner stated that therefore, the invention as a whole is prima facie obvious over Pollman et al. and Gibbons et al. in view of Manoharan et al.

In response, without conceding the correctness of the Examiner's position, applicant has amended claims 9, 26 and 36. As amended, claims 9, 26 and 36 are not obvious over Pollman et al., Manoharan et al. and Gibbons et al. as the combination of

references does not teach all of the characteristics recited in the amended claims. Specifically, there is no teaching of any of SEQ ID NOS: 1 or 3-13 in the references cited by the Examiner. Applicant also notes that there is little predictability as to whether a given antisense oligonucleotide will function as such, and, consequently, each novel oligonucleotide needs to be tested for efficacy, for example see **Exhibit B**, especially the last paragraph at page 641 continuing over to page 642.

Applicants further note that new claims 63-65 are also not obvious over Pollman et al., Manoharan et al. and Gibbons et al. Specifically, the references cited by the Examiner fail to teach an oligonucleotide consisting of amino acids having the sequence set forth in SEQ ID NO:2. Applicants note that the sequence taught in Pollman et al. is longer than SEQ ID NO:2.

Accordingly, applicant requests that the examiner withdraw the grounds of rejection set forth in the Office Action and earnestly solicit allowance of the pending claims.

Figures

Applicants attach hereto as **Exhibit C** formal drawings numbered 6, 7 and 21 with corrections as requested by the draftsperson.

If a telephone interview would be of assistance in advancing prosecution of the subject application, applicant's undersigned attorneys invite the Examiner to telephone them at the number provided below.

No fee is deemed necessary in connection with the filing of this Supplemental Amendment. However, if any such fee is required, authorization is hereby given to charge the amount of any such fee to Deposit Account No. 03-3125.

Respectfully submitted,

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I hereby certify that this correspondence is being deposited this date with the U.S. Postal Service with sufficient postage as first class mail in an envelope addressed to:
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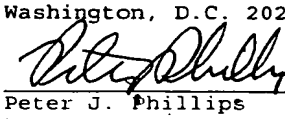

10-24-02

Peter J. Phillips Date
Reg. No. 29,691

Mark Up copy of Amendments to the Claims

Claims 9, 26 and 36 have been amended as follows:

--9. (2X Amended) A composition of matter comprising an antisense oligonucleotide comprising consecutive nucleotides, the nucleotide sequence of which is set forth in one of SEQ ID NOS: 1 and 3-13 [1-13], wherein one or more sugar of the oligonucleotide contain an -OMe group at its 2' position.--

--26. (2X Amended) A method of promoting the regression of vascular lesions, comprising introducing into a vascular cell an amount of a composition of matter comprising an antisense oligonucleotide comprising consecutive nucleotides, the nucleotide sequence of which is set forth in one of SEQ ID NOS: 1 and 3-13 [1-13], effective to reduce the levels of bcl-xL protein produced, thereby promoting the regression of vascular lesions, wherein one or more sugar of the oligonucleotide contain an -OMe group at its 2' position.--

--36. (Amended) A composition of matter comprising an antisense oligonucleotide comprising consecutive nucleotides, the nucleotide sequence of which is set forth in one of SEQ I NOS: 1 and 3-13 [1-13], wherein one or more sugar of the oligonucleotide is modified at its 2' position.--